The Clinical and Laboratory Response to Recombinant Factor VIIa in Trauma and Surgical Patients with Acquired Coagulopathy

Neil R. McMullin, MD, David S. Kauvar, MD, Heather M. Currier, MD, Toney W. Baskin, MD, Anthony E. Pusateri, PhD, and John B. Holcomb, MD

United States Army Institute of Surgical Research, Fort Sam Houston, Texas

OBJECTIVE: In bleeding patients who are coagulopathic, the clinical response to administration of recombinant factor VIIa (rFVIIa) relates to the changes in prothrombin time (PT).

DESIGN: Retrospective review of all surgical and trauma patients who were coagulopathic and received factor VIIa at the authors' institution over the past 27 months.

SETTING: Academic tertiary referral facility and level I trauma center.

PARTICIPANTS: Eighteen patients met inclusion criteria, 10 trauma and 8 surgical. Mean age 50 years (range, 17-84).

RESULTS: Overall mortality was 39%. All but 1 patient (17/18) had resolution of coagulopathic bleeding with rFVIIa, and all clinical responders (n = 17) (defined as clinical cessation of bleeding within 24 hours determined by either attending surgeon or chief resident progress note) had a decrease in PT to normal range. In contrast, the single clinical nonresponder had an insignificant PT decrease (19 to 18 seconds). Prothrombin time decreased from 20 ± 4 seconds to 12 ± 2 seconds, $p < 0.05$ (n = 17). International Normalized Ratio (INR) decreased from 1.59 to 0.86, $p < 0.05$ (n = 17). Fibrinogen before administration was 299.73 (range, 105-564) (n = 15). pH before administration was 7.25 (±0.18) (n = 10). Patient temperature was 98.64 (±2.06). Effect in partial thromboplastin time (PTT) was inconsistent (50 ± 49 seconds to 34 ± 6 seconds, $p > 0.05$). Transfusion requirements for red blood cells (14 to 3 units) and plasma (12 to 3 units) were significantly reduced after rFVIIa. There were no significant differences in percentage PT decrease between dose ≥100 mcg/kg vs <100 mcg/kg, surgical vs trauma patients, survivors vs nonsurvivors, and those with pretreatment platelet count ≥100 K vs <100 K.

CONCLUSIONS: The administration of rFVIIa caused a decrease in the PT in nearly all patients. There were an insufficient number of patients to support the use of PT as a clinical predictor of response; however, the data are suggestive of such utility. If the PT does not correct, then it is likely that there is a deficiency of other factors of the coagulation cascade. (Curr Surg 63:246-251. © 2006 by the Association of Program Directors in Surgery.)

KEYWORDS: coagulopathy, hemorrhage, trauma, recombinant factor VIIa, thromboembolism

INTRODUCTION

The "lethal triad" of hypothermia, acidosis, and coagulopathy poses a significant problem in the care of critically ill surgical patients. The sequential and additive effect of these 3 conditions perpetuates a vicious cycle associated with increased mortality.[1] Once this downward spiral has initiated, it is difficult, if not impossible, to interrupt. Standard transfusion therapy is often inadequate to deal with the challenges of the progression of acquired coagulopathy.

In 1990, recombinant factor VIIa (rFVIIa, Novoseven; Novo Nordisk, Bagsvaerd, Denmark) was introduced for the treatment of hemophilia. The use of rFVIIa for the correction of acquired coagulopathy and treatment of traumatic hemorrhage was first reported in 1999.[2] Since then, the off-label use of rFVIIa for the treatment of coagulopathic hemorrhage secondary to major surgery and trauma has been the subject of limited retrospective series.[3-5] The agent has also shown promise in experimental animal models of severe traumatic hemorrhage.[6-10] A recent multicenter study of rFVIIa demonstrated decreased blood product usage in blunt-trauma patients with traumatic hemorrhage.[11]

The above studies of the efficacy of rFVIIa in treating coagu-

Correspondence: Inquiries to Neil R. McMullin, MD, U.S. Army Institute of Surgical Research, 3400 Rawley E. Chambers Avenue, Building 3611, Fort Sam Houston, TX 78234-6315; e-mail: john.holcomb@amedd.army.mil

Presented at the 27th Annual Gary P. Wratten U.S. Army Surgical Symposium in El Paso, Texas, April 25, 2005.

0149-7944/06/$30.00
doi:10.1016/j.cursur.2006.03.007

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 JUL 2006	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
The clinical and laboratory response to recombinant factor VIIA in trauma and surgical patients with acquired coagulopathy	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
McMullin N. R., Kauvar D. S., Currier H. M., Baskin T. W., Pusateri A. E., Holcomb J. B.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX 78234	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**SAR**	**6**	

lopathy have primarily examined surrogate endpoints such as blood product usage and the response of laboratory tests of coagulation to drug administration. There are few published data regarding the clinical response to the drug. Clinically relevant endpoints are the cessation of bleeding, restoration of hemodynamic stability, and survival. There is little discussion in the literature relating the laboratory response to the clinical response. The relationship of laboratory response to clinical outcomes has not been addressed. The elucidation of these relationships will allow for further refinement of the use of this expensive but promising agent in various patient populations.

The data were retrospectively analyzed on the use of rFVIIa in trauma and surgical patients with acquired coagulopathy at the authors' institution to examine the relationship between the clinical and laboratory responses to the drug. It was hypothesized that the laboratory response to a dose of rFVIIa in a bleeding, coagulopathic patient could be used to predict a clinical response.

METHODS

After approval from the Brooke Army Medical Center IRB, all patients who had received rFVIIa at this institution between January 1, 2002 and March 31, 2005 were identified. A total of 34 charts were reviewed. Patients who had received the drug for intracranial hemorrhage (n = 3), known hemophiliacs (n = 1), patients with pharmacologic anticoagulation (warfarin, heparin) at the time of rFVIIa administration (n = 3), those without coagulopathy (n = 2), burn patients (n = 1), and patients whose charts had incomplete data (n = 8) were excluded. The result was a population of 18 patients. Demographic data, laboratory results, blood product usage, and physician's notes were examined.

A guideline was used for the administration of rFVIIa to patients without a known inherited coagulopathy. The medication can be given as an adjunct to resuscitation at the request of an attending physician to a patient that has continued coagulopathy with clinical evidence of hemorrhage despite massive resuscitation as defined by greater than 10 units of red blood cells, 8 units of fresh frozen plasma, and an apheresis pack of platelets. In this series, there was 1 patient, who because of religious constraints, declined all blood products. Recombinant FVIIa was given on a "compassionate use" basis where no blood products were administered. A clinical response was defined as occurring in those patients who were deemed by the chief surgical resident or attending surgeon to be without evidence of continued hemorrhage and to be hemodynamically stable within 24 hours of their dose of rFVIIa. Prothrombin Time and partial thromboplastin time (PTT) (normal range, 12.0-14.3 and 24.2-37.2 seconds, respectively) were measured by the hospital laboratory using standard assays.

Data from patient records were compiled in a database (Excel; Microsoft, Redmond, WA). Statistical analysis was carried out using SigmaStat Statistical Software version 2.0 (SPSS, Inc, Chicago, IL). Means were compared using the Student *t*-test for normally distributed data and the Mann–Whitney rank sum test for non-normally distributed data. Statistical significance was defined as $p < 0.05$ throughout.

TABLE 1. Laboratory Response (mean ± SD) to rFVIIa in Patients with Acquired Coagulopathy

	PT (seconds)	PTT (seconds)
Pre-rFVIIa	20 ± 4	50 ± 49
Post-rFVIIa	12 ± 2*	34 ± 6
Absolute change	8 ± 4	16 ± 49
Percent change	38	10

*$p < 0.05$ compared with pre-rFVIIa.

RESULTS

A total of 18 patients met inclusion criteria and were included in the analysis. Their mean age was 50 years (range, 17-80). There were 10 trauma patients with a mean Injury Severity Score of 29 ± 10. Eight trauma patients had sustained blunt trauma, and 2 had penetrating trauma. Of particular note, 1 blunt trauma patient was a Jehova's Witness who refused all blood transfusion. He had sustained a severe pelvic fracture with arterial hemorrhage. Recombinant factor VIIa was administered after angiography with arterial embolization was performed. The surgical patients either had hemodynamically significant gastrointestinal bleeding requiring surgery or had undergone a major surgical procedure. Procedures performed included pancreaticoduodenectomy with portal vein reconstruction, abdominal aortic aneurism repair, abdominoperineal resection, and retroperitoneal placement of a central venous access device.

The mean dose of rFVIIa was 100 ± 20 mcg/kg. The overall mortality was 7/18 (39%). No complications were attributable to the administration of rFVIIa. All but 1 patient in this series was determined to be free of continued hemorrhage and became hemodynamically stable after the administration of rFVIIa. The overall mortality of the responders was 35%. As a note of interest, the Jehova's Witness patient was a responder and ultimately a survivor. The single nonresponder was a 74-year-old woman who had undergone a significant small bowel resection for infarcted bowel. This patient did not survive. Because of the existence in this series of only a single nonresponder, direct comparisons could not be performed between those patients who responded clinically and those that did not.

All patients were coagulopathic, exhibiting abnormal PT at the time of administration of rFVIIa. Pre- and post-dose laboratory coagulation parameters are presented in Table 1. The PT decreased an average of 38% with the administration of rFVIIa ($p < 0.05$), and all but the 1 patient who failed to respond clinically experienced a decrease into the normal range as defined by the authors' institution (12-14.3 seconds). The nonresponder experienced only a marginal decrease in the PT (19-18 seconds) and remained above the normal range. The effect of rFVIIa on PTT was more variable, and 3 patients experienced

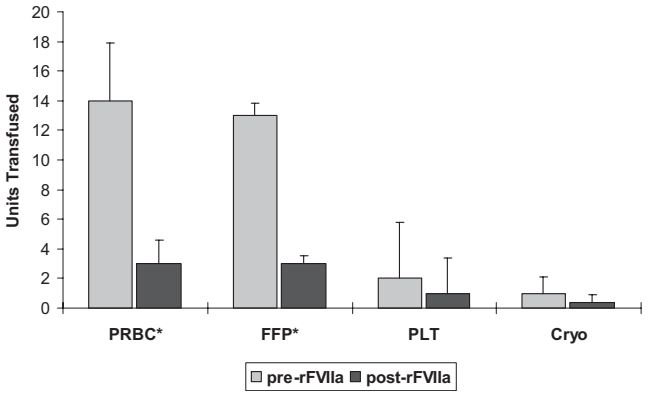

FIGURE 1. Blood product use (mean ± standard error) before and after administration of rFVIIa. Note: *$p < 0.05$ for difference between pre- and post-value with dose. Abbreviations: Cryo, cryoprecipitate; PLT, platelet; PRBC, packed red blood cell.

an increase in PTT. The mean decrease in PTT was only 10%, and the nonresponder experienced a decrease of only 4 seconds (55-51 seconds). The INR is a value that is calculated based on the PT. Consequently, this value will reflect changes observed in PT. These data were consistent with this observation; the pre-dose INR in this responder population was 1.59 (± 0.4) and decreased to 0.86 (± 0.19) ($p < 0.05$). This single nonresponder had a pre-dose INR of 1.6 and a post-dose of 1.5. The pH of this responder population, although these data are unavailable, is 7.23 (± 0.19) ($n = 10$). This nonresponder had a pre-dose pH of 7.37.

Blood product use before and after administration of rFVIIa is presented in Fig. 1. The mean pre-dose packed red blood cell transfusion was 15.8 units (range, 1-49 units), which decreased significantly to 3.6 (0-10) units after the administration of rFVIIa ($p < 0.05$). Transfusion of fresh frozen plasma (FFP) also decreased significantly, from a mean of 17 units (3-46) to 3 units (0-26, $p < 0.05$).

In an attempt to determine factors influencing the change in PT with rFVIIa administration, candidate data points were stratified and univariate analyses were performed on their effect on the percentage change. Stratification was performed as follows: dose ≥ or <100 mcg/kg, pre-rFVIIa FFP ≥ or <12 units (mean pre-dose FFP administration was 12 units of FFP), pre-rFVIIa administration of cryoprecipitate, surgical versus trauma, and survivor versus nonsurvivor. There were no significant differences in percent PT change between any of these subgroups. The results of the univariate analyses are presented in Table 2.

DISCUSSION

In this series, 94% of patients with coagulopathy demonstrated marked decreases in their PT with administration of rFVIIa and were hemodynamically stable within 24 hours of administration. The single patient that did not respond clinically also failed to experience a significant drop in the PT. The PTT results in this series were inconsistent and thus unreliable in monitoring the activity of rFVIIa.

Prothrombin time is a clot-based assay performed on citrated plasma. The assay takes 5 minutes to perform; however, logistical considerations drive local turn-around times. The clotting reaction is initiated by adding a source of tissue factor (TF) and phospholipids (usually in the form of thromboplastin) and calcium. By the most common method, the time to clot formation is determined by the change in turbidity as the fibrin mesh forms. Because the assay specifically examines the TF pathway, it is sensitive to rFVIIa. The maximal degree of PT shortening is limited not only by *in vivo* parameters but also by the concentration of TF and phospholipids present in the assay reagents and by the settings of the instrument, which may have a minimum clot time, such as 8 seconds, that can be reported. A frequent result after rFVIIa treatment is that the PT is shortened to the maximal degree detectable by the assay. This assay is sensitive to both temperature and pH. Standard PT assays are run at 37°C, and the pH is dictated by the reagents used. Therefore, the correction in PT may not reflect the actual status of the patient under coagulopathic condition. Some automated instruments now perform PT at the temperature of the patient, which assists in interpretation.

It has been demonstrated that PT is improved after rFVIIa administration to trauma patients, regardless of whether they respond in terms of *in vivo* hemostasis.[4,12,13] Similar observations have been made regarding the PT and hemostatic responses to rFVIIa in patients with liver disease[14] and platelet disorders[15] and in animal studies.[9] These findings suggest that the usefulness of the PT as an indicator of rFVIIa efficacy in surgery may be questionable. However, there is some indication that the degree of shortening of the PT may be related to efficacy. Although the PT shortened in all patients after rFVIIa, Dutton et al[4] found that the post-rFVIIa PT was shorter in patients that responded hemostatically than in those

TABLE 2. Results of Univariate Analysis of Possible Predictors of Change in PT

	Dose (mcg/kg)		Pre-rFVIIa FFP		Pre-rFVIIa Cryo		Patient Type		Outcome	
	<100	<100	<12 units	≥12 units	Yes	No	Trauma	Surgical	Lived	Died
PT Change	37%	37%	42%	35%	38%	37%	39%	35%	38%	37%
p	0.96		0.34		0.86		0.49		0.87	

NOTE: Changes in PT are expressed in percentage drop from the pre-administration of rFVIIa level.
Abbreviation: Cryo, cryoprecipitate.

TABLE 3. Thromboembolic Adverse Events Published in Randomized, Blinded, Placebo Controlled Trials

Reason for Use	Control % (AE/# Subjects)	rFVIIa Treated % (AE/# Subjects)
Surgery[20,21]	7 (9/130)	10 (25/253)
Intracranial bleeding[22]	2 (2/96)	7 (21/303)
Trauma[11]	4 (6/138)	4 (6/139)
Liver transplant[23]	11 (2/19)	8 (5/64)
Cardiopulmonary bypass[24]	20 (2/10)	22 (2/9)
Upper gastrointestinal bleeding[25]	6 (7/121)	6 (7/121)
Total	5 (28/514)	7 (66/889)

that did not. Martinowitz and Michaelson[13] reported that PT was shortened from 18.2 to 10.7 seconds within 15-20 minutes of rFVIIa administration in trauma patients that responded hemostatically to the drug. The PT was also shortened in hemostatic nonresponders, from 28.5 to 20 seconds, but the PT of very few of these patients approached the normal range after rFVIIa.

In the current study, the mean improvement in PT after rFVIIa administration (from 20 to 12 seconds) was similar to that reported by Martinowitz and Michaelson for patients that responded hemostatically. The 17 patients that experienced improved hemostasis in response to rFVIIa all had PT that were corrected into the normal range, whereas the PT in the patient that did not experience improved hemostasis shortened only slightly, failing to approach the normal range.

Based on currently available data, it is believed that the PT may be of use in identifying those patients who will not respond as desired to an appropriate dose of rFVIIa. If PT is not shortened after rFVIIa administration, replacement of 1 or more components in addition to rFVIIa may be indicated.

Although the PT may not be the ideal test to monitor rFVIIa function, it is relatively fast and of value. These data suggest that if the PT fails to normalize with the administration of rFVIIa, the patient may not resolve their coagulopathic bleeding. Such a failure may reflect a deficiency of 1 or more of the other coagulation factors. If the PT does respond, however, and continued hemorrhage is evident, then the source of such bleeding may be surgical in nature, or may be caused by platelet deficiency or dysfunction.

Many published uses of rFVIIa other than the treatment of inherited disorders of coagulation have been in the face of severe, life-threatening coagulopathy. In this series, the drug was effective in ceasing coagulopathic bleeding in these situations in nearly all cases. The administration of rFVIIa to patients who do not have significant acquired coagulopathy but are likely to require transfusion is now being studied in a prospective fashion. Friederich et al[16] showed a significant decrease in perioperative blood loss and transfusion of red blood cells in patients who received a dose of rFVIIa before undergoing elective retropubic prostatectomy. These data suggest that there may be benefit to the administration of rFVIIa before coagulopathy ensues in patients in whom a large volume of blood loss may be imminent. If administered before the onset of acidosis, dilution, and hypothermia in trauma patients, rFVIIa may have a transfusion-avoiding effect, thus avoiding further complications and risks associated with blood product transfusion.[17,18] Continuing prospective study of the utility of rFVIIa before the onset of coagulopathy is merited.

This study has several limitations, including all of those applicable to the use of retrospective methodology. In addition, the lack of nonresponders, although suggesting appropriate use of the rFVIIa administration guidelines, made it impossible to compare the characteristics of patients who respond clinically and those who do not. Further randomized, double-blinded, placebo-controlled trials are recommended with evaluation of clinical endpoints to further study the efficacy of recombinant activated factor VII.

These and existing published data support the need for additional research regarding the possible role that rFVIIa can fulfill as a viable adjunct for the treatment of severe acquired coagulopathy when used in conjunction with surgical correction of hemorrhage, warming, and appropriate resuscitation in an intensive care unit setting. The use of a clinical endpoint defined by the evaluation by surgical staff allowed for a focused assessment of outcome other than blood use. The PT seems to be the best widely available laboratory measure of coagulation for monitoring the response and activity of rFVIIa.

There has been an exponential increase in the off-label use of rFVIIa over the past 5 years. With increased use, there is increased attention regarding possible serious adverse events associated with administering this potent modulator of the coagulation system. A recent article published by O'Connell et al[19] from the Food and Drug Administration focuses on serious thromboembolic adverse events (AEs) reported to the FDA's Adverse Events Reporting System (AERS). The focus of this article is the off-label use of rFVIIa and the number of serious thromboembolic events reported through this system. Table 3 details the 7 published randomized controlled trials studying off-label use of rFVIIa.[20-25] Listed is the incidence of serious thromboembolic events in the treatment and placebo arms of each study. This table is not intended to be a meta-analysis of these studies. As opposed to the self reported registry from which the O'Connell et al article bases its analysis, these articles go into detail about the clinical situation in which the AE occurred and have control groups, allowing knowledge of the incidence of the AE's in the target population. Reporting the occurrence of thromboembolic AEs without showing the results of a placebo arm only tells half of the story and does not portray a balanced view. Without proper control groups for

comparison, these articles should be considered at best a series of case reports and not used for definitive risk assessment. It would be premature to draw conclusions regarding the safety of rFVIIa from the data presented in the O'Connell et al article without discussing all 7 prospective, controlled trials that have been published. The safety information in current published data from randomized, blinded controlled studies suggests that rFVIIa does not have an increased thromboembolic AE complication rate compared with placebo controls. Institutional Review Boards across the country are now considering studies to evaluate the next clinical question, namely, is this drug effective? This question is currently being addressed by an ongoing phase III trial throughout North America.

ACKNOWLEDGMENTS

The authors wish to acknowledge Mrs. Nancy C. Molter, RN, PhD, Mrs. Audrey V. Parker, and Mrs. Monica DeWitte for their assistance with this work.

REFERENCES

1. MacLeod JB LM, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. *J Trauma*. 2003;55:39-44.
2. Kenet G, Walden R, Eldad A, Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet*. 1999;354:1879.
3. Dutton RP, Hess JR, Scalea TM. Recombinant factor VIIa for control of hemorrhage: early experience in critically ill trauma patients. *J Clin Anesth*. 2003;15:184-188.
4. Dutton RP, McCunn M, Hyder M, et al. Factor VIIa for correction of traumatic coagulopathy. *J Trauma*. 2004; 57:709-719.
5. Geeraedts LM Jr, Kamphuisen PW, Kaasjager HA, Verwiel JM, van Vugt AB, Frolke JP. The role of recombinant factor VIIa in the treatment of life-threatening haemorrhage in blunt trauma. *Injury*. 2005;36:495-500.
6. Jeroukhimov IJD, Zaias J, Hensley G, et al. Early injection of high-dose recombinant factor VIIa decreases blood loss and prolongs time from injury to death in experimental liver injury. *J Trauma*. 2002;53:1053-1057.
7. Lynn MJI, Jewelewicz D, Popkin C, et al. Early use of recombinant factor VIIa improves mean arterial pressure and may potentially decrease mortality in experimental hemorrhagic shock: a pilot study. *J Trauma*. 2002;52:703-707.
8. Martinowitz UHJ, Pusateri AE, Stein M, et al. Intravenous rFVIIa administered for hemorrhage control in hypothermic coagulopathic swine with grade V liver injuries. *J Trauma*. 2001;50:721-729.
9. Schreiber MA HJ, Hedner U, Brundage SI, Macaitis JM, Hoots K. The effect of recombinant factor VIIa on coagulopathic pigs with grade V liver injuries. *J Trauma*. 2002; 53:252-259.
10. Sondeen JL, Pusateri AE, Hedner U, Yantis LD, Holcomb JB. Recombinant factor VIIa increases the pressure at which rebleeding occurs in porcine uncontrolled aortic hemorrhage model. *Shock*. 2004;22:163-168.
11. Boffard KD, Riou B, Warren B, et al. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma*. 2005; 59(1):8-15; discussion 15-18.
12. Eikelboom JW, Bird R, Blythe D, et al. Recombinant activated factor VII for the treatment of life-threatening haemorrhage. *Blood Coagul Fibrinolysis*. 2003; 14:713-717.
13. Martinowitz U, Michaelson M. Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force. *J Thromb Haemost*. 2005;3:640-648.
14. Jeffers L, Chalasani N, Balart L, Pyrsopoulos N, Erhardtsen E. Safety and efficacy of recombinant factor VIIa in patients with liver disease undergoing laparoscopic liver biopsy. *Gastroenterology*. 2002;123(1):118-126.
15. Almeida AM, Khair K, Hann I, Liesner R. The use of recombinant factor VIIa in children with inherited platelet function disorders. *Br J Haematol*. 2003;121: 477-481.
16. Friederich PW, Henny CP, Messelink EJ, et al. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial. *Lancet*. 2003;361:201-205.
17. Hamilton S. The use of blood in resuscitation of the trauma patient. *Can J Surg*. 1993;36(1):21-27.
18. Ferrara A, Wright JM, Modlin HK, McMillen MA. Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. *Am J Surg*. 1990;160: 515-518.
19. O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA*. 2006;295: 293-298.
20. Lodge JP, Jonas S, Jones RM, et al. Efficacy and safety of repeated perioperative doses of recombinant factor VIIa in liver transplantation. *Liver Transpl*. 2005;11:973-979.
21. Lodge JP, Jonas S, Oussoultzoglou E, et al. Recombinant coagulation factor VIIa in major liver resection: a random-

ized, placebo-controlled, double-blind clinical trial. *Anesthesiology*. 2005;102:269-275.

22. Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2005;352:777-785.

23. Planinsic RM, van der Meer J, Testa G, et al. Safety and efficacy of a single bolus administration of recombinant factor VIIa in liver transplantation due to chronic liver disease. *Liver Transpl*. 2005;11:895-900.

24. Diprose P, Herbertson MJ, O'Shaughnessy D, Gill RS. Activated recombinant factor VII after cardiopulmonary bypass reduces allogeneic transfusion in complex non-coronary cardiac surgery: randomized double-blind placebo-controlled pilot study. *Br J Anaesth*. 2005;95:596-602.

25. Bosch J, Thabut D, Bendtsen F, et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. *Gastroenterology*. 2004;127:1123-1130.